Review:
Teratogenic Causes of Malformations

Enid Gilbert-Barness
Department of Pathology, Tampa General Hospital and University of South Florida College of Medicine, Tampa, Florida

Abstract. Crucial morphogenetic processes during the blastogenesis period, which extends throughout the first 4 wk of development, from fertilization until the end of the gastrulation stage (days 27 to 28 postconception), can be altered and result in structural abnormalities, including patterns of multiple congenital anomalies (MCAs) arising from developmental field defects. Severe damage may cause death of the product of conception or, because of the pluripotential nature of the cells, the damage may be compensated allowing development to continue in a normal fashion. Most investigators believe that the all-or-none rule applies to the first 2 wk of development. Because the fetus is less susceptible to morphologic alterations when the developmental process of the majority of organs has been completed, the most common anomalies associated with teratogenic exposures during the fetal period are fetal growth restriction (intrauterine growth retardation) and mild errors of morphogenesis (abnormalities of phenogenesis), such as epicanthic folds, clinodactyly, and others. Thus, teratogenic exposures result in a wide variety of effects that range from infertility, prenatal onset growth restriction, structural defects, and functional CNS abnormalities to miscarriage or fetal death.

Keywords: teratogens, malformations, disruptions, morphogenesis, environmental exposures

Introduction
It is estimated that approximately 10-15% of congenital structural anomalies are the result of the adverse effect of environmental factors on prenatal development [1]. This means that approximately 1 in 250 newborn infants have structural defects caused by an environmental exposure and, presumably, a larger number of children have growth retardation or functional abnormalities resulting from nongenetic causes, in other words, from the effects of teratogens. A teratogen is defined as any environmental factor that can produce a permanent abnormality in structure or function, restriction of growth, or death of the embryo or fetus. A dose-response relationship should be demonstrated in animals or humans so that the greater the exposure during pregnancy, the more severe the phenotypic effects on the fetus [2]. Factors comprise medications, drugs, chemicals, and maternal conditions or diseases, including infections. Time of exposure and specificity are shown in Table 1. This manuscript discusses the teratogenic effects of well-documented environmental factors.

Brent [1] noted that it is inappropriate to label an agent as teratogenic without characterizing the dose, route of exposure, and stage of pregnancy when the exposure occurred. This is because, as has long been recognized, the effects of an environmental agent on the embryo or fetus depend on the chemical or physical nature of the agent and several other factors, such as dose, route, and length of exposure.
exposure; the developmental stage at which the exposure occurs; the genetic susceptibility of the mother and embryo or fetus; and the presence and nature of concurrent exposures [3].

Teratogenic exposures during prenatal development cause disruptions regardless of the developmental stage or site of action. Most structural defects caused by teratogenic exposures occur during the embryonic period, which is when critical developmental events are taking place and the foundations of organ systems are being established [4]. Different organ systems have different periods of susceptibility to exogenous agents.

**Radiation**

Ionizing radiation can injure the developing embryo due to cell death or chromosome injury. There is no proof that human congenital malformations have been caused by diagnostic levels of radiation. The most critical exposure period is 8-15 wk after fertilization [5,6]. Before implantation, the mammalian embryo is insensitive to the teratogenic and growth-retarding effects of radiation and sensitive to the lethal effects [7-9]. The risks of 1-rad (0.10Gy) or 5-rad (0.05Gy) acute exposure are far below the spontaneous risks of the developing embryo because 15% of human embryos abort, 2.7 - 3.0% of human embryos have major malformations, 4% have intrauterine growth retardation, and 8-10% have early- or late-stage onset genetic disease. Permanent growth retardation is more severe after midgestation radiation.

Because of its extended periods of organogenesis and histogenesis, the central nervous system (CNS) retains the greatest sensitivity of all organ systems to the detrimental effects of radiation through the later fetal stages. In utero radiation produces microcephaly and mental retardation. Later in life there is increased incidence of hematopoietic malignancies and leukemia [10].

**Infectious Agents**

The lethal or developmental effects of infectious agents are the result of mitotic inhibition, direct cytotoxic effects, or a vascular disruptive event on the embryo or fetus. However, a repair process may result in scarring or calcification, which causes further damage by interfering with histogenesis [11,12]. Infections that do not result in congenital malformations but do cause fetal or neonatal death include enteroviruses (coxsackievirus, poliovirus, and echovirus) and hepatitis, variola, vaccina, and mumps viruses [13,14]. Non-radioactive in-situ hybridization of formalin-fixed, paraffin-embedded placental and fetal tissue, using virus-specific DNA or RNA probes, is helpful for diagnosing fetal virus infections such as cytomegalovirus, parvovirus B-19, and varicella-zoster virus that cause fetal hydrops, placentitis, and abortion [15].

**Varicella.** Varicella (or chickenpox) is a highly infectious disease, usually occurring in childhood. By adulthood, more than 95 percent of Americans have had chickenpox. Eighty-five to ninety-five

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**Table 1. Time specificity of action of some human teratogens [190].**

<table>
<thead>
<tr>
<th>Teratogen</th>
<th>Fertilization Age (days)</th>
<th>Malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella virus</td>
<td>0-60</td>
<td>Cataract or heart diseases more likely</td>
</tr>
<tr>
<td></td>
<td>0-&gt;129</td>
<td>Deafness</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>21-40</td>
<td>Reduction defects of extremities</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>18-30</td>
<td>Anencephaly</td>
</tr>
<tr>
<td>Male hormones</td>
<td>&lt;90</td>
<td>Clitoral hypertrophy and labial fusion</td>
</tr>
<tr>
<td>(androgens)</td>
<td>&gt;90</td>
<td>Clitoral hypertrophy</td>
</tr>
<tr>
<td>Warfarin (coumadin)</td>
<td>&lt;100</td>
<td>Hypoplasia of nose and stippling of epiphyses</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>&gt;=14</td>
<td>Possible mental retardation</td>
</tr>
<tr>
<td></td>
<td>&gt;=58</td>
<td>50% vaginal adenosis</td>
</tr>
<tr>
<td>Radioiodine therapy</td>
<td>&gt;=126</td>
<td>50% vaginal adenosis</td>
</tr>
<tr>
<td>Goitrogens and iodides</td>
<td>&gt;=180</td>
<td>10% vaginal adenosis</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>&gt;=120</td>
<td>Dental enamel staining of primary teeth</td>
</tr>
<tr>
<td></td>
<td>&gt;=150</td>
<td>Staining of crowns of permanent teeth</td>
</tr>
</tbody>
</table>
percent of pregnant women are immune to chickenpox, which means that there is no need to be concerned about this during pregnancy, even if the woman is exposed to someone with chickenpox. Nearly seven women out of 10,000 will develop chickenpox during pregnancy, however, because they are not immune [16].

The disease is caused by the varicella-zoster virus (VZV), which is a form of the herpes virus. Transmission occurs from person-to-person by direct contact or through the air. Chickenpox is contagious from 1 to 2 days before the appearance of the rash until the blisters have dried and become scabs. Once a person is exposed to the virus, chickenpox may take up to 14 to 18 days to develop. When a woman has a varicella infection during the first 20 wk of pregnancy, there is a 2% chance that the baby will have a group of defects called the congenital varicella syndrome [16], which includes scars, defects of muscle and bone, malformed and paralyzed limbs, small head size, blindness, seizures, and mental retardation. This syndrome is rarely seen if the infection occurs after 20 wk of pregnancy.

Another time that there is a concern about a varicella infection is in the newborn period, if the mother develops the rash during the period from 5 days before to 2 days after delivery. Between 25% and 50% of newborns will be infected in this case, and they develop a rash between 5 and 10 days after birth. Up to 30% of infected babies will die if not treated. If the mother develops a rash between 6 and 21 days before delivery, the baby faces some risk of mild infection [17].

If the baby is treated immediately after birth with an injection of VZIG (varicella-zoster immune globulin), the infection can be prevented or the severity lessened [16]. If a pregnant woman has been exposed to someone with chickenpox, VZIG can be given within 96 hr to prevent chickenpox or lessen the severity [16]. It is important for pregnant women to avoid exposure to anyone with chickenpox if they are unsure that they are immune to this infection.

**Mumps virus.** Mumps virus during pregnancy does not cause malformations, but endocardial fibroelastosis has been noted in infants with a positive mumps antigen skin test; this relationship has not been consistent [18].

**Influenza virus.** There is no compelling evidence to incriminate influenza virus infection during pregnancy as a cause of malformations [18].

**Parvovirus.** Human parvovirus B-19 is able to cross the placenta and result in fetal infection, which may occur whether the mother is symptomatic or asymptomatic. It is associated with a higher than average fetal loss and may lead to spontaneous abortion in the first trimester, hydrops fetalis in the second trimester, and stillbirth at term [19,20]. Generalized myocarditis, myositis of skeletal muscles, and abnormalities of the eyes are reported [21]. Human parvovirus B-19 has an affinity for the erythropoietic tissue of the host and is therefore associated with fetal anemia leading to cardiac failure.

**Other viral infections.** Other viruses have not resulted in congenital anomalies but have caused significant fetal pathology. Poliovirus has been associated with abortion, stillbirth, and meningomyelitis [22]; echovirus with disseminated viremia [23]; variola and vaccinia with necrotizing cutaneous and visceral infection; and hepatitis virus with neonatal hepatitis [24].

**Syphilis.** It is believed that the fetus cannot be infected with syphilis early in pregnancy because a cytotoephoblastic layer of cells in the chorionic villi of the placenta prevents the spirochete from passing from maternal to fetal blood. This cell layer disappears at the sixth month. Since the spirochete usually does not reach the conceptus during the first trimester, it is usually not a cause of abortion [25]. However, there has been a report of syphilitic endometritis causing first trimester abortion as a potential infectious cause of fetal morbidity in early gestation [26].

In untreated maternal syphilis of less than 2 yr duration, about half of the infants are live-born without infection. In untreated maternal syphilis in the primary or secondary stages, 50% are stillborn or die within 4 wk after birth. In untreated maternal syphilis in the early part of the tertiary stage, 20% to 60% of infants are normal,
40% have congenital syphilis, 20% are born prematurely, and 16% are stillborn or die within 4 wk after birth. In untreated syphilis in the late part of the tertiary stage, 75% of babies are unaffected, 10% have congenital syphilis, 9% are born prematurely, 10% are stillborn, and 1% die within 4 wk after birth [27].

**Toxoplasmosis.** Primary maternal infection with *Toxoplasma gondii* occurs in 1 per 1000 pregnancies in the United States [28]. Infection is disseminated through the placenta to the offspring in 40%, with maternal infection through the placenta. Malformations do not occur; however, hydrocephalus and microcephaly result from chronic destructive meningoencephalitis. Chorioretinitis may progress to scarring and loss of vision. Hydrocephalus and cerebral calcifications, hepatitis, and lymphadenopathy are the most common complications in infants infected prenatally [29]. Organisms have been recovered from the brain of a congenitally infected infant after 5 yr.

**Therm disruptions**

**Hyperthermia** is defined as a body temperature of at least 38.9°C and is an antimitotic teratogen after exposure between weeks 4 and 14 [30-32]. In a retrospective study, Smith et al [33] presented 21 patients who had been exposed during pregnancy to hyperthermia caused by infections or by sauna bathing. Severe mental deficiency, seizures in infancy, microphthalmia, midface hypoplasia, and mild distal limb abnormalities were associated with hyperthermia [33]. Infants exposed to maternal hyperthermia at 7 to 16 wk of gestation have hypotonia, neurogenic arthrogryposis, or CNS dysgenesis [34]. Shiota [34] studied 100 embryos with CNS defects and found that 18% of mothers of anencephalic infants had experienced hyperthermia at the critical embryonic stage [34]. Occipital encephalocele has also been related to hyperthermia [35]. Embryonic studies in guinea pigs and rats have highlighted the sensitivity of brain growth to elevated temperatures [36-38].

**Hypothermia** is defined as a core body temperature of less than 35°C. Cardiopulmonary bypass in a pregnant patient is associated with a fetal mortality rate of 16% to 33%. One infant with multiple congenital defects has been described. Another infant had severe disruptive defects of the brain and distal spinal cord, suggesting hypoperfusion injuries related to hypothermia [39].

**Toxic Metals**

**Lead.** A woman who has had lead poisoning can pass lead on to her fetus if she becomes pregnant, even if she no longer is exposed to lead. This happens because more than 90% of the lead may be stored in bone and released into the bloodstream years later. Blood Pb levels of ≥10 µg/dl are considered to be elevated but not dangerously high. The term “lead poisoning” refers to blood Pb levels ≥50 µg/dl. Deleterious effects of lead exposure have not been convincingly shown to occur at blood Pb levels ≤20 µg/dl. Lead crosses the placenta as early as the 12th to 14th weeks of gestation and accumulates in fetal tissue [40-42]. The adverse effects of lead include spontaneous abortion and stillbirth. A small but significant increase in minor malformations, including hemangiomas, lymphangiomas, hydroceles, skin tags, skin papillae, and undescended testes, was seen in infants with high lead levels in the umbilical blood [41-44]. The VACTERL (vertebral, anal, cardiac, tracheoesophageal fistula, renal and limb abnormalities) association has been reported with prenatal exposure to high lead levels, similar to animal models of lead teratogenicity [45].

**Mercury.** Organic forms of mercury are more toxic than the inorganic forms. Methylmercury, the most toxic organic form, causes severe brain damage, as in Minamata disease, which occurred in epidemic proportions on the Japanese island of Minamata after maternal ingestion (by both humans and cats) of methylmercury-contaminated shellfish [46]. A similar exposure occurred in Iraq after the ingestion of bread prepared from wheat treated with methylmercury that was used as a fungicide [47]. The blood Hg assay measures exposure to all types of mercury, but because mercury remains in the bloodstream for only a few days after exposure, the test should be done soon
after exposure. Most non-exposed people have blood Hg levels of 0 to 2 µg/dl. Levels >2.8 µg/dl are required to be reported to the state health department. The assay can be influenced by eating fish that contain mercury. Early effects of mercury toxicity have been found when the blood Hg level exceeds 3 µg/dl [48]. Methylmercury poisoning produces atrophy of the granular layer of the cerebellum and spongiose softening in the visual cortex and other cortical areas of the brain [47]; polyneuritis can also occur.

**Lithium** is used in the treatment of bipolar disorder. If possible lithium should be withheld during the first trimester of pregnancy and women taking lithium should not breast feed their infants. The ratio of lithium concentrations in umbilical cord blood to maternal blood is uniform (mean 1.05 ± 0.13). Infants with high lithium concentrations (>0.64 mmol/L) at delivery have significantly lower Apgar scores. High lithium concentrations at delivery are associated with perinatal complications, and lithium concentrations can be reduced by brief suspension of therapy proximate to delivery. Cardiovascular malformations, in particular Ebstein anomaly and tricuspid atresia, have been related to lithium exposure [49-52]. Infants exposed in utero to lithium may experience transient lethargy, hypotonia, cyanosis, poor feeding, and poor respiratory efforts during the early neonatal period [49]. Other defects that have been noted in infants exposed to lithium in utero include malformations of the CNS, ear, and ureter, altered thyroid and cardiac function, and congenital goiter [53]. Some abnormalities (mainly heart defects such as Ebstein malformation) in the newborn occur in 6% to 10% of pregnancies involving first-trimester exposure to lithium [54,55].

**Chemical Exposures**

**Polychlorinated and polybrominated biphenyls (PCBs).** PCBs have been used for more than 40 years as insulating fluids, heat exchangers, plasticizers, and chemical additives, and they are known to be worldwide pollutants. They have been present in game fish caught in PCB-contaminated waters [56]. Placental transfer of PCBs occurs in humans [57]. Women suffering from PCB poisoning have infants with parchment-like skin with desquamation and brown discoloration (“cola baby”), dark colored nails, conjunctivitis, low birthweight, exophthalmos, and natal teeth. Reduced birthweight and small head size with hypotonicity and hyporeflexia are associated with higher levels of exposure. There is no evidence of reproductive risk to humans as long as occupational exposures to PCBs are below the recommended airborne levels of 0.0001 mg/m³ [58]. PCBs may interfere with male reproductive function by exerting estrogenic agonist/antagonist activity. **Toluene.** Standards for a permissible exposure limit (PEL) for toluene have been set by the U.S. Occupational Safety and Health Administration (OSHA) at 100 ppm (375 mg/m³), calculated as a time weighted average over an 8-hr workday. Toluene embryopathy includes prenatal and postnatal growth deficiency, microcephaly, anencephaly, developmental delay, cardiac and limb defects, and craniofacial anomalies similar to fetal alcohol syndrome (FAS) [57,59-67]. Pheno-otypic facial abnormalities similar to those of FAS suggest a common mechanism of craniofacial teratogenesis for toluene and alcohol attributed to deficiency of craniofacial neuroepithelium and mesodermal components due to increased embryonic cell death [67].

**Maternal Conditions**

**Obesity.** During pregnancy, obesity is associated with adverse outcomes that include macrosomia, hypertension, pre-eclampsia, gestational diabetes mellitus (GDM), and fetal death [68-72]. In addition, many investigators have reported an increased risk of birth defects.

**Diabetes mellitus.** Although hyperglycemia may be key in the pathogenesis of diabetic embryopathy, other factors contained in diabetic serum may also contribute to the embryopathy [73]. Hyperglycemia leads to inhibition of the myoinositol uptake that is essential for embryonic development during gastrulation and neurulation stages of embryogenesis [74,75]. Deficiency of myoinositol appears to cause perturbations in the phosphoinositide system that lead to abnormalities in the arachidonic acid-prostaglandin pathway. The gastrulation and
neurulation stages of development are particularly sensitive to hypoglycemia and result in growth retardation as well as cranial and caudal neural tube defects (NTDs). Obesity that occurs with a number of metabolic abnormalities, including abnormal glucose metabolism, is associated with a higher risk of malformations. A possible role of free oxygen radicals in diabetic teratogenicity has been suggested. The pathogenesis of diabetic embryopathy is heterogeneous [73,74]; maintenance of glucose homeostasis is important for the prevention of diabetic embryopathy.

There is a correlation between elevated hemoglobin A1c (HbA1c) levels and the incidence of major congenital anomalies in infants of diabetic mothers (IDMs) [76-80]. HbA1c is a normal, minor hemoglobin that differs from HbA by the addition of a glucose moiety to the amino-terminal valine of the beta chain. Glycosylation of hemoglobin A occurs during circulation of the red cell and depends on the average concentration of glucose to which the red cell is exposed during its life cycle [81]. Measurement of HbA1c provides an index of chronic glucose elevation, and therefore of diabetes control [82]. HbA1c levels during pregnancy that exceed 11.5% are associated with congenital abnormalities in 66% of the offspring, but levels below 9.5% are not associated with increased frequency of anomalies in infants of diabetic mothers [83]. Defects of the heart, central nervous system (CNS), kidneys, and skeleton predominate. Transposition of the great vessels, ventricular septal defect (VSD), and dextrocardia occur with greatest frequency. Anencephaly, spina bifida, and hydrocephaly are the major CNS malformations. Rare malformations include situs inversus and caudal dysplasia, vertebral and renal anomalies, imperforate anus, radius aplasia, renal abnormalities including agenesis and dysplasia, and other defects. Brain development is often impaired and anomalies include those observed in the VACTERL association. Minor physical abnormalities include anteverted nares, flattened nasal bridge, excess skin folds on the neck, and tapered fingers with hyperconvex nails. Other complications include hyperbilirubinemia, hypocalcemia, vascular thromboses (eg, renal vein thrombosis), and respiratory distress syndrome.

Caudal dysplasia syndrome, with varying degrees of sacral agenesis, is sometimes associated with defects of the palate and branchial arches and occurs in 1% of diabetic offspring [84,85].

Hypothyroidism in infants occurs when the fetal thyroid gland has been suppressed by antithyroid drugs (propylthiouracil, carbimazole, iodides), radioactive iodine [86] or possibly maternal antibodies [87]. Transfer of maternal thyroxin to the fetus is negligible during early pregnancy. During the final weeks of pregnancy, thyroid-binding globulin (TBG) may compete for thyroxin. Triiodothyronine is less bound by TBG and can more freely cross the placenta.

Hyperthyroidism during pregnancy is usually due to Graves disease. The presence of thyroid-stimulating globulins may result in thyrotoxicity in the fetus and newborn regardless of the treatment of maternal disease. Neonatal thyrotoxicosis is usually a transient phenomenon lasting several months. Affected infants have goiter, exophthalmos, restlessness, tachycardia, periorbital edema, ravenous appetite, hyperthermia, cardiomegaly, cardiac failure, and hepatosplenomegaly [88].

Hyperparathyroidism. Infants of mothers with untreated hypoparathyroidism may have transient hyperparathyroidism during the fetal and neonatal periods [89]. The fetal parathyroid hyperplasia that occurs in response to low maternal and fetal serum calcium concentration is mediated by the maternal parathyroid dysfunction. Bone demineralization and subperiosteal reabsorption occurs in the long bones. IUGR, pulmonary artery stenosis, VSD, and muscle hypotonia also occur.

Cretinism and iodine deficiency. Iodine deficiency is the cause of endemic goiter and cretinism due to deficiency or of insufficient availability of thyroxine at the feto-placental level. There is a role of maternal T4 in neurological embryogenesis, before the onset of fetal thyroid function and, therefore, its protective role in fetal thyroid failure. In early pregnancy, iodine deficiency induces a critical decrease of T4 levels with consequent TSH increase responsible for hypothyroidism in about 50% of iodine-deficient pregnant women. Congenital
hypothyroidism associated with deafness and mental retardation is found in the offspring of hypothyroid mothers. Deafness persists in spite of thyroid replacement therapy. Developmental changes in the brain and cerebellum have been described [90].

Fetal iodine deficiency results in cretinism characterized by mental retardation, spastic diplegia, deafness, and strabismus [91,92]. It requires severe maternal iodine deficiency (less than 20 µg/day) during the first half of gestation, which occurs primarily in Northern Italy and in mountainous areas of New Guinea, the Himalayas, and the Andes.

Myotonic dystrophy. The myotonic dystrophy gene contains a segment of CTG repeats that tends to amplify in each generation [87-89]. Infants born of women with myotonic dystrophy may show fetal hypokinesia and generalized weakness, and may experience difficulty in respiration and feeding. The facies characteristically shows tenting of the upper lip, ptosis, absence of movement, and anterior cupping of the pinnas. Clubfoot is often present and postnatal growth is slow.

Phenylketonuria. Maternal phenylketonuria (PKU) leads to defects that include intrauterine
and postnatal growth retardation, cardiovascular defects, dislocated hips, and other anomalies [93-95]. Infants of mothers with PKU are heterozygous, and because phenylketonuric heterozygotes are generally normal, the defect in the fetus must be attributed to the maternal metabolic disturbance. These effects are directly related to the maternal phenylalalnine level. When the level exceeds 20 mg/ml, 92% of infants have mental retardation; 73%, microcephaly; 40%, IUGR; and 12%, cardiac malformations. One-fourth of pregnancies abort spontaneously.

Ethanol, Smoking, and Various Drugs

Fetal Alcohol Syndrome (FAS). Patients with FAS must have three characteristics: prenatal and postnatal growth retardation (>2 SD for length and weight), facial anomalies, and CNS dysfunction (Table 2). The full picture of FAS usually occurs in babies born to alcoholic mothers, or those who drink regularly or binge-drink. However, no amount of alcohol is safe. Even light or moderate drinking can affect the developing fetus. Acetaldehyde is implicated as the cause of FAS through its inhibiting effects on DNA synthesis, placental amino acid transport, and development of the fetal brain [96-98]. The biologic basis for FAS is related to genetic polymorphisms identified for alcohol dehydrogenase (ADH), which converts alcohol to acetaldehyde, and acetaldehyde dehydrogenase (ALDH2), which converts acetaldehyde to acetate. Genetic differences in ADH alleles make some infants exposed to the same level of alcohol in utero more likely to have longer or higher levels of exposure to acetaldehyde. This may explain the greater frequency in American blacks and Native Americans.

Structural and functional impairments occur in up to one half of infants born to alcoholic women who drink heavily. Functional and growth disturbances without other morphologic changes can occur in infants whose mothers drink moderately (1 to 2 oz of absolute ethanol daily). No malformations have been documented in infants of mothers who drink <1 oz of absolute ethanol daily. However, the risk of spontaneous abortion is twice the normal rate in women who drink 1 oz of ethanol twice a week [99]. Binge drinking in the first trimester may be a cause of fetotoxicity [100]. In view of the limited understanding of the effects of prenatal exposure to alcohol, abstinence from alcohol during pregnancy is a wise precaution.

Chloroquine. Minimal knowledge is available of the effects of chloroquine malarial prophylaxis used during pregnancy. Van Allen and colleagues [101] studied the effects of chloroquine on women in Tanzania who were taking 500 mg/wk from the time they became pregnant. Malformations in three half-siblings included up-slanting palpebral fissures, flat philtrum, thin upper lip, and brachydactyly of the fifth finger. Maternal chloroquine use during pregnancy may be associated with auditory, vestibular, retinal, and other neurologic dysfunction in children.

Tobacco smoking. Nicotine is a vasoconstrictor that results in uterine vascular constriction and intrauterine growth retardation (IUGR) through decreased perfusion of fetal tissues [102]. It is a cholinergic agonist and a constituent of tobacco. Cigarette smoking during pregnancy raises the risk of perinatal mortality and morbidity [103]. The increased mortality is attributed to abruptio placentae, placenta previa, spontaneous abortion, prematurity, and IUGR [104].

Carbon monoxide from cigarette smoke also crosses the placenta and produces an increase in blood carboxyhemoglobin (HbCO) levels; there is a longer half-life of HbCO in fetal blood than in maternal blood [105-107].

Marijuana. The active ingredient of marijuana is 8,9-tetrahydrocannabinol, which is fat soluble, crosses the placenta easily, and may persist in the fetus for as long as 30 days [108-110]. Growth retardation and malformations are reported after marijuana use during pregnancy, especially in the first trimester. However, other potentially teratogenic drugs are often used by women who smoke marijuana. Increased risk of nonlymphoblastic leukemia has been reported [111].

Lysergic acid diethylamide (LSD). Children born to mothers who used LSD before or during pregnancy have had a variety of anomalies. Defects
of the limbs, eyes, CNS, and arthrogryposis may be present [112]. The assessment of the effects of LSD use during pregnancy has been difficult, since the women’s lifestyle may include use of alcohol and other drugs, poor medical care, and malnutrition. There is no indication that the risk of congenital anomalies is great [113]. LSD-induced chromosomal damage may last up to 2 years but is sometimes transient [114,115]. There is no evidence that paternal exposure to LSD in small doses before conception is associated with increased rates of spontaneous abortion, premature birth, or birth defects [116,117].

**Sedatives.** Increased frequencies of cleft lip, cleft palate, and congenital heart disease have been reported after maternal phenobarbital exposure [118]. Benzodiazepine-containing drugs, taken in large amounts, may produce IUGR, cleft lip, and facial features that resemble the findings of FAS [2,119], although studies have shown little or no increase in congenital anomalies.

**Isotretinoin** (accutane, retin-A, retinoic acid) (Table 3). The risk of fetal abnormality when isotretinoin is taken by a pregnant woman is 25% [118]. The critical period of exposure is 4 to 10 wk of gestation. The defects include hydrocephalus, microcephaly, cerebellar dysgenesis, depressed nasal bridge, microtia or absent external ears, cleft palate, anomalies of the aortic arch, cardiac defects (including ventricular septal defect, atrial septal defect, tetralogy of Fallot), and hypoplastic adrenal cortex [120-122]. Spontaneous abortion is also increased. A pregnancy-prevention program has been implemented in women of child-bearing age receiving isotretinoin [123]. Use of topical retinoic acid has not been associated with fetal malformations. Like its congener isotretinoin, etretinate is bound to lipoproteins and persists in the circulation for years after use.

**Thalidomide** (Table 4). Thalidomide was used clinically in the 1960s. It caused limb reduction defects, facial hemangiomas, esophageal and duodenal atresia, cardiac defects (eg, tetralogy of Fallot), renal agenesis, urinary tract anomalies,

### Table 3. Manifestations in isotretinoin embryopathy [192].

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Hydrocephalus, leptomeningeal, heterotopias, Dandy-Walker, corticospinal tract malformations</td>
</tr>
<tr>
<td>Brain (occasional)</td>
<td>Gyral defects including grade 3 lissencephaly, regional pachygyria, subcortical heterotopias</td>
</tr>
<tr>
<td>Brain function</td>
<td>Severe or profound mental retardation, hypotonia, diminished deep tendon reflexes (absent or abnormal)</td>
</tr>
<tr>
<td>Craniofacial</td>
<td>Low-set, small or atretic, malformed ears; small or atretic external auditory meatus; microphthalmia; telecanthus; epicanthal folds; low nasal bridge; small jaw, sometimes with U-shaped cleft palate (Robin sequence)</td>
</tr>
<tr>
<td>Heart</td>
<td>Ventricular septal defect, truncus arteriosus, double-outlet right ventricle; interrupted aortic arch; patent ductus arteriosus</td>
</tr>
</tbody>
</table>

### Table 4. Abnormalities in thalidomide embryopathy [193]

<table>
<thead>
<tr>
<th>Skeletal defects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent radii</td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td></td>
</tr>
<tr>
<td>Limited extension, club hand, hypoplastic or fused phalanges, finger syndactyly, carpal hypoplasia or fusion, radial deviation</td>
<td></td>
</tr>
<tr>
<td>Ulna</td>
<td></td>
</tr>
<tr>
<td>Short and malformed, unilaterally or bilaterally absent</td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td></td>
</tr>
<tr>
<td>Hypoplastic, absent</td>
<td></td>
</tr>
<tr>
<td>Shoulder girdle</td>
<td></td>
</tr>
<tr>
<td>Abnormally formed with absent glenoid, fossa and acromion process, hypoplastic scapula and clavicle</td>
<td></td>
</tr>
<tr>
<td>Hips</td>
<td></td>
</tr>
<tr>
<td>Unilaterally or bilaterally dislocated</td>
<td></td>
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<tr>
<td>Legs</td>
<td></td>
</tr>
<tr>
<td>Coxa valga, femoral torsion, tibial torsion, bilateral or unilateral stiff knee, abnormal tibiofibular joint, dislocated patella(e)</td>
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<tr>
<td>Feet</td>
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<tr>
<td>Overriding fifth toe, calcaneovalgus deformity</td>
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<tr>
<td>Ribs</td>
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<tr>
<td>Asymmetric first rib, cervical rib</td>
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<tr>
<td>Spine</td>
<td></td>
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<tr>
<td>Cervical spina bifida, fused cervical spine</td>
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<tr>
<td>Mandibular hypoplasia</td>
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<tr>
<td>Maxillary hypoplasia</td>
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<tr>
<td>Cardiac anomalies</td>
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<tr>
<td>Tetralogy of Fallot, atrial septal defect, patent foramen ovale, dextrocardia, congestive heart failure leading to death</td>
<td></td>
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<tr>
<td>Systolic murmur, cardiomegaly</td>
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<tr>
<td>Suspected congenital heart disease</td>
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<tr>
<td>Other abnormalities</td>
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<tr>
<td>Apparently low-set ears, malformations extending to microtia</td>
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<tr>
<td>Urogenital anomalies</td>
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<tr>
<td>Meckel diverticulum</td>
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<td>Uterine anomalies</td>
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genital defects, dental anomalies, ear anomalies, facial palsy, ophthalmoplegia, anophthalmia, microphthalmia, and coloboma [125,126]. Cleft palate was a rare occurrence and the CNS was not affected. The children had normal intelligence. The sensitive period for production of human thalidomide birth defects was 23 to 28 days postconception, with the critical period no longer than 14 days. About 20% of pregnancies exposed during this period resulted in infants with anomalies, the most notable of which were limb defects ranging from triphalangeal thumb to tetra-amelia or phocomelia of the upper and lower limbs, at times with preaxial polydactyly of six or seven toes per foot [125].

McCredie [127-129] postulated interference with neural crest-based sclerotomal organization as the pathogenetic basis of the limb malformations. McCredie and coworkers [125,130] expanded their studies of the visceral anomalies in infants who died with multiple congenital anomalies with longitudinal limb defects by attempting to determine whether neural crest injury would impair development of structures supplied by the sensory autonomic nerves derived from the injured zone of the neural crest. Application of sclerotomal and viscerotomal maps to the autopsy data showed a neuroanatomic correlation in 89% of cases. The authors proposed a developmental correlation within a multiple congenital anomaly syndrome on the basis of neurotomes or embryonic developmental fields with common regional innervation. Thalidomide is an inhibitor of angiogenesis; its antiangiogenic activity correlates with its teratogenicity [131].

**Folic acid deficiency and folic acid antagonists.** Folic acid deficiency has been observed in a high percentage of women who have had infants with a neural tube defect (NTD); folic acid antagonists also may result in NTDs. Deficiency of folic acid appears to result in up to 70% of NTDs, particularly anencephaly [132]. The US Food and Drug Administration (FDA) recommends fortifying food with adequate levels of folic acid. Periconceptional daily intake of 0.4 mg of folic acid (the dose commonly contained in over-the-counter multivitamin preparations) reduces the risk of NTDs by approximately 60% [133]. The US Public Health Service (PHS) recommends that all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day in order to reduce their risk of having a pregnancy affected with spina bifida or other NTDs [134]. Because the effects of high intakes are not well known but include masking the diagnosis of vitamin B12 deficiency, care should be taken to keep total folate consumption at <1 mg per day. Women who had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregnancy.

**Ergotamine.** Ergotamine is a natural alkaloid of ergot that causes smooth muscle contraction. The constrictive effects of ergotamine on fetal blood vessels may be responsible for IUGR and jejunal atresia [135]. No adverse effect on pregnancy was found in women who took ergotamine for the treatment of migraine [136,137]. A report from the database of the Hungarian Case-Control Surveillance of Congenital Anomalies (1980-1986) showed that of 9460 children born to mothers exposed to ergotamine in the first 3 months of pregnancy, three had NTDs [136]. Controlled studies on ergotamine use during pregnancy have not been reported.

**Metronidazole (Flagyl).** Metronidazole is an antibiotic and antiprotozoal agent commonly used to treat gynecologic infections. It has been associated with birth defects in isolated cases [138]. However, most published reports indicate that use of this drug during pregnancy is not associated with an increase of malformations, spontaneous abortions, stillbirths, or prematurity [139-141].

**Cocaine.** Cocaine is metabolized very slowly in the fetus because the fetus has low plasma cholinesterase activity [142]. Cocaine blocks the presynaptic reuptake of neurotransmitters at nerve terminals, which results in increased levels of norepinephrine and dopamine [143]. It may alter the availability and utilization of calcium, and reduce blood flow from the uterus to the placenta. The complications of abruptio placentae, cerebral hemorrhage, IUGR, limb defects, bowel atresia, and necrotizing enterocolitis appear to be related to vascular
disruption [144]. Cocaine-exposed fetuses also have increased incidences of prematurity, microcephaly, and sudden infant death [145].

**Phenytoin (hydantoin, dilantin).** Phenytoin is a medication used to treat epilepsy. If taken by the mother in the first trimester, there is a small risk for a combination of birth defects known as the fetal hydantoin syndrome. The pattern of anomalies consists of developmental delay or frank mental deficiency, dysmorphic craniofacial features, and hypoplasia of the distal phalanges. The presence of major phenytoin-associated birth defects in a child correlates with an inability of lymphocytes to detoxify the drug. There appears to be genetic susceptibility to phenytoin fetal toxicity. Twins have been discordant for manifestations of the hydantoin syndrome [146]. The risk of developmental disturbance in phenytoin-exposed children ranges from 1% to 11%. Chronic exposure presents a maximum of 10% risk for the full syndrome and a maximum of 30% risk for some anomalies [147,148].

**Trimethadione, paramethadione.** Maternal use of these drugs results in spontaneous abortion in one-fourth of pregnancies. Most liveborn infants have prenatal and postnatal growth deficiency, developmental delay, malformations, and distinctive facies, including brachycephaly with midfacial hypoplasia, V-shaped eyebrows with or without synophrys, broad nasal bridge, arched or cleft palate, and malpositioned ears, with anterior cupping and/or excessive folding of the superior helices [149]. Cardiovascular defects, particularly septal defects and tetralogy of Fallot, renal malformations, tracheoesophageal anomalies, hernias, and hypospadias are common. Survivors often have mild to moderate mental retardation and speech impairment [149].

**Warfarin (dicumarol, coumarin derivatives).** Women with a history of thromboembolic disease or artificial heart valves often require long-term anticoagulant therapy. There is an estimated 25% risk for affected infants after exposure during the period from 8 to 14 weeks of pregnancy. Warfarin inhibits the formation of carboxyglutamyl from glutamyl residues, decreasing the ability of proteins to bind calcium [150]. Calcific stippling occurs primarily in the tarsals, proximal femurs, and paravertebral processes. Brachydactyly and small nails, with greater severity in the upper limbs, has been present in about one-half of affected infants. Optic atrophy, microphthalmia and blindness can result from exposure during the first or second trimester. Brain anomalies include microcephaly, optic atrophy, visual impairment, seizures, hypotonia, and mental retardation. Inhibition of calcium binding by proteins during a critical period of ossification may explain the nasal hypoplasia, stippled calcification, and skeletal abnormalities of warfarin embryopathy [150].

**Angiotensin-converting enzyme (ACE) inhibitors.** Captopril crosses the human placenta. Its use and that of other ACE inhibitors is associated with spontaneous abortions, intrauterine and neonatal deaths, neonatal respiratory distress, limb and CNS defects, patent ductus arteriosus (PDA), oligohydramnios, and calcarial hypoplasia, as well as renal tubular dysplasia [151].

**Statins.** The statins are hypolipidemic drugs used to lower serum cholesterol levels in people who have or are at risk for cardiovascular disease [152,153]. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes formation of mevalonate from HMG-CoA, the rate-limiting step in the mevalonate pathway of cholesterol biosynthesis. Cholesterol, an integral part of cell membranes, is critical for embryonic and fetal development. It also is the precursor of steroid hormones and is essential for the activation and propagation of hedgehog signaling, which regulates critical events during development, including patterning of the CNS [154-157]. The FDA designated these drugs in pregnancy category X [153] and, therefore, their use is contraindicated in women who are or may become pregnant. Because approximately 50% of pregnancies in the United States are unplanned [158-160], early pregnancies may be unknowingly exposed to them.

Because of the recognition of various patterns of congenital abnormalities (CA) resulting from
deficient de novo cholesterol synthesis [161-163], concern has been raised about the potential effect of prenatal use of statins on embryonic and fetal development. These patterns include the Smith-Lemli-Opitz syndrome; two Smith-Lemli-Opitz-like syndromes, desmosterolosis and lanosterolosis; and two skeletal dysplasia syndromes with dermatologic manifestations, X-linked dominant chondrodysplasia punctata type 2 and congenital hemidysplasia with ichthyosiform erythroderma and limb defects (Child syndrome) [162,163]. At present, no controlled studies have shown teratogenicity of statins in humans. However, case reports [164,165] and a case series reported by Edison and Muenke [166] have suggested that statins may have teratogenic effects.

**Assisted Reproductive Technologies**

In addition to the problems inherent in multiple pregnancies, children conceived by assisted reproductive technologies (ART) have increased risks for low-birth weight (LBW) and preterm delivery [2,167,168]. Data on birth defects are inconclusive because most available studies, which generally are observational and based on small sample sizes, do not have the power to control for confounding factors, such as parental age, causes of infertility, the multiple technical variables of the ART regimens, and the causal heterogeneity of infertility [169-172]. In contrast to early reports showing a lack of association between ART and an increased rate of birth defects [173-177], more recent and larger studies [178-183], including three meta-analyses [184-186], indicate that children conceived by ART are more likely to have a CA than children conceived spontaneously. Anomalies with the strongest associations include hypospadias and other genitourinary defects. Nasal tube defects (NTDs), gastrointestinal anomalies, CHDs, and chromosomal abnormalities may occur [178-183]. Hansen et al [184] reviewed 25 reported studies; two-thirds of them showed 25% or greater risk for birth defects in children conceived by ART.

**Examples of Nonteratogenic Agents**

**Spermicides.** Spermicides are agents that impair the ability of sperm to fertilize an egg. This suggests that spermicides should not affect the developing pregnancy, since their task is to prevent pregnancy to begin with. Studies during the 1970s and 1980s suggested that spermicides might cause some birth defects. Subsequent studies, however, have shown no association between the use of spermicides and an increased risk for birth defects [2,187].

**Acetaminophen.** Acetaminophen is the active ingredient of some pain relievers. Thousands of women have taken acetaminophen-containing pain relievers during pregnancy and there has been no association with an increased risk of birth defects, when used at or below the recommended dosage [2,188].

**Prenatal vitamins.** Vitamins are prescribed when a woman becomes pregnant to supplement her diet to meet the growing nutritional needs of pregnancy. The amounts of vitamins contained in prenatal vitamin pills are calculated to address some of the biological changes that happen when a woman is pregnant, such as increased blood volume. When used at the recommended dosage, prenatal vitamins do not increase the risk of birth defects [2,189].

**Microwave ovens.** There are two types of radiation: ionizing and non-ionizing radiation. X-rays are an example of ionizing radiation, while ultraviolet rays (sunlight) and microwaves are examples of non-ionizing radiation. Non-ionizing radiation is not teratogenic. Microwaving of food during pregnancy is not known to increase the risks for birth defects or health problems [2].

**Summary**

This manuscript summarizes the well-documented teratogenic causes of fetal malformations due to prenatal exposures and includes some examples of agents that have been suspected but are found to be nonteratogenic.

**References**


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